Journal of Surgical Oncology 1997;66:81–87

# The Impact of Residual Disease on Local Recurrence in Patients Treated by Initial Unplanned Resection for Soft Tissue Sarcoma of the Extremity

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**Background and Objectives:** "Unplanned excision" in soft tissue sarcoma (STS) is defined as the gross removal of tumor without preoperative staging or consideration of the need for removal of normal tissue around the tumor. This study evaluated whether unplanned excision in patients with extremity STS would have an impact on local relapse (LR), even if reexcision of the tumor bed was undertaken.

**Method:** Two hundred thirty-nine (239) patients with primary, extremity STS treated with limb salvage surgery were included in this study. Of the 239, 78% were treated with surgery and irradiation. Forty-seven tumors were low-grade and 192 high grade. Mean tumor diameter was 7.5 cm. Twenty had local recurrences and 64 relapsed systemically.

**Results:** Only margin and prior surgery were significant in univariate analysis ($P < 0.05$, log-rank test). The Cox multivariate analysis revealed that both margin of resection ($P < 0.001$) and the status of the local tumor site ($P < 0.05$) at definitive surgery were significant predictors of local relapse.

**Conclusions:** These results suggest that the presence of microscopic disease in the reexcised specimen following unplanned resection is a risk factor for local disease recurrence.

*J. Surg. Oncol. 1997;66:81–87.* 

KEY WORDS: **soft tissue tumor; treatment; prognosis**

## INTRODUCTION

Much of the progress made in the local management of extremity soft tissue sarcoma (STS) results from the ability of surgical and radiation oncologists to accurately assess the extent of disease invasion in the limb using both clinical examination and CT and MRI imaging modalities [1–9]. Using these staging modalities we have shown that it is possible to control local disease in 95% of patients referred to our center prior to removal of their tumors [9]. However, the ability to accurately assess the extent of disease is diminished when the patient has undergone complete excision of the macroscopic lesion prior to referral to the cancer center.

Giuiliano and Eilber introduced the term "unplanned excision" for the operation performed for gross removal

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Accepted 26 June 1997

of a soft tissue sarcoma without regard for preoperative imaging or the necessity to remove a margin of normal tissue covering the cancer [10]. Usually the surgeon performing an unplanned resection has not anticipated the diagnosis of soft tissue sarcoma and does not attempt to perform a complete excision of the tumor with adequate margins. Clinical investigations in our unit have shown that if all patients referred following unplanned excision were subsequently treated with reexcision of the previously operated tumor bed, residual sarcoma was identified in at least 35% of cases [5], and other authors have discovered an even higher incidence of residual sarcoma [4,5,11,12].

The purpose of this article was to evaluate whether unplanned excision of an extremity STS, even if reexcision of the tumor bed were undertaken, was a predictor of local recurrence.

## MATERIALS AND METHODS

From our prospective database, all patients treated by a single surgeon (RSB) with limb sparing surgery for STS of the extremity between January 1986 and February 1994 were identified. This period represents commencement of the treating surgeon's subspecialty practice with minimum follow-up of 2 years for all patients. The extremity was defined as extending from the medial border of the scapula to the finger tips for the upper extremity and from the outer wing of the ilium to the toes for the lower extremity. Patients presenting to our center with a local recurrence were eligible for the study providing their prior treatment did not include radiotherapy. Exclusion criteria included: (1) metastatic disease at presentation; (2) amputation; (3) STS occurring in a previously irradiated field; (4) histological subtype of rhabdomyosarcoma or peripheral neuroectodermal tumor (PNET); and (5) treatment with adjuvant chemotherapy. Two hundred and forty patients were eligible for this study but one patient was lost to follow-up immediately following treatment and has been excluded from the analysis, leaving a sample of 239 patients. Forty-nine extremity patients treated with surgery during this time period were ineligible: 8 who developed an STS in a previous radiation field; 17 who required amputation; 5 with lung metastases at presentation; 5 who presented with a locally recurrent STS that had undergone prior radiation therapy and surgery elsewhere for the initial lesion; and 14 who had rhabdomyosarcoma or PNET and/or received adjuvant chemotherapy.

All patients were seen in consultation in a multidisciplinary clinic by a radiation oncologist and a single surgical oncologist involved in definitive treatment. Following initial examination at our center, all patients underwent staging with local imaging (CT or MRI scan), chest CT, and review of pathology. When a patient had undergone excision of the gross tumor mass prior to referral, the pathology from the initial surgery was reviewed and data from the original surgical and pathology reports [4] was evaluated to determine the status of the original surgical margins. All consultation patients who had been treated elsewhere with surgery resulting in definitely negative resection margins received no further surgical treatment at our center and are, consequently, not included in this study. Patients who had undergone resection elsewhere with positive resection margins were treated with reexcision of the total tumor bed. For the purposes of this study, we referred to the initial surgery as an "unplanned resection."

If the patient had not been operated on prior to referral, biopsy material was obtained at our center using needle biopsy in most cases. If needle biopsy was insufficient for diagnosis, or if the anatomical location prevented needle biopsy, open incisional biopsy was performed prior to confirming the plan for definitive therapy.

All patients were discussed at a multidisciplinary conference (radiology, pathology, medical, surgical and radiation oncology, and allied health personnel) prior to initiation of treatment. At this conference it was decided whether adequate treatment would require irradiation as well as surgery (i.e., combined management) based on the anatomic constraints of obtaining a wide, curative local resection. Irradiation prior to surgery was advised only if it was obvious that combined management would be required and one of the following factors was present: (1) the location and size of the tumor would make it technically more difficult to provide optimal irradiation treatment after excision as the proposed surgery would significantly increase the size of the radiation field; (2) dissection would be along a major neurovascular bundle with the possibility of leaving microscopic disease on these critical structures; or (3) the surgeon expected that remote tissue flaps or skin grafts would be necessary for wound management following resection.

Patients receiving preoperative irradiation were treated to 50 Gy in 25 fractions over 5 weeks. The irradiation field encompassed the tumor and a 5-cm margin. In patients treated with preoperative irradiation, a postoperative boost of 16 Gy was recommended if resection margins were positive.

In the remaining patients, the recommendation for postoperative radiotherapy was based on the evaluation of the surgical specimen. If there was any gross or microscopic evidence of sarcoma present within 2 cm of the resection margin, postoperative radiotherapy was generally recommended using 60 to 66 Gy in 2 Gy daily fractions. The irradiation field encompassed the operative field and a 5-cm margin or an uninterrupted fascial plane using a shrinking field technique [9].

Surgery was planned to obtain a wide resection with negative tumor margins whenever possible. If the sarcoma abutted a major neurovascular structure, the struc-

ture was generally preserved with epineurium being stripped off the nerve where possible [4]. If these neurovascular structures were embedded in gross disease, the nerve or vessel was resected and reconstructed if possible. Irradiation, as described, was used when wide surgical margins could not be achieved.

Pathological evaluation of the resected tumor and/or tumor bed was carried out in a standardized fashion. To ensure that the specimen was oriented and processed appropriately, the surgeon always examined the specimen with the pathologist in the frozen section suite of the operating room. Following orientation of the specimen, the tissue was serially sliced (at approximately 1-cm intervals) and the tumor was sampled. Representative sections were taken from all resection margins. If prior unplanned resection had been performed, the prior surgical site was identified and multiple sections were taken from this region of the prior resection bed as previously described [5]. Pathological evaluation was done by one pathologist.

Recognizing that the local recurrence rate for extremity soft tissue sarcoma is at least 5–10% [7,9], it was anticipated that there would be 20–25 local recurrences in this patient series. Concato et al. [13] suggest that a minimum of 10 events per variable are required when analyzing predictive models and a priori two variables were chosen for evaluation in the statistical model. The primary hypothesis was that margin and the status of the local tumor site would be predictive of time to local recurrence. (Time zero was taken as the date of definitive surgery.) Surgical margin was defined as microscopic positive of the pathologist found tumor at the inked margin of the specimen [8,9]. The status of the local tumor site at the time of definitive surgery was categorized in three levels: (1) tumor in situ at presentation to our center (an incisional biopsy may have been done); (2) prior unplanned resection with positive margins and microscopic disease found in the specimen on pathological review; and (3) prior unplanned resection with positive margins and no microscopic disease found in the specimen on pathological review.

All analyses were completed using the statistical package Stata 4.0 (Stata Corporation, College Station, TX). Descriptive summary statistics included means, standard deviations, and frequencies. Kaplan-Meier estimates of time to local recurrence and the log-rank test were used for univariate analysis. The assumption of the proportional hazard function, that is that the risk of local recurrence is the same over the time period, was tested for each of margin and status of the tumor site by using the variable*log(time) form for each variable; proportionality was then tested by comparing the models using the likelihood ratio test. Variables significant at the $p = 0.05$ level in the univariate analysis, including time-varying covariates where indicated, were used in the multivariate Cox model.

Finally, in an exploratory analysis, tumor grade coded as low grade or high grade, size as $\leqslant 5$ cm or $>5$ cm and depth were evaluated as described above.

## RESULTS

Sample characteristics presented in Table I demonstrate that this sample is typical of the extremity STS population with a mean age of 56.2 years and slightly more males than females. Malignant fibrous histiocytoma (38.9%) followed by liposarcoma (26.7%) were the most frequent subtypes. Forty-seven (19.7%) tumors were low grade and 192 (80.3%) were high grade. The maximum tumor diameter was $\leqslant 5$ cm in 133 (55.6%) and greater than 5 cm in 106 (44.4%) [14]. Tumor size was determined from the pathological specimen in 185 cases, from radiological studies in 11 cases, and 43 cases were based on clinical estimation. Fifty-two lesions were superficial and 187 were deep.

Radiotherapy was used in 186 (77.8%) cases; 95 preoperative only, 55 postoperative only, and 36 preoperative with a postoperative boost. One hundred and thirty-five (56.5%) patients presented with mass in situ, 42 (17.6%) had prior unplanned resections and microscopic disease was found in the reresection specimen, and 62 (25.9%) had prior unplanned resections and no microscopic disease was found. One hundred and ninety-four (81.2%) patients had their tumors resected with negative margins and 45 (18.8%) had positive margins.

Mean follow-up of the 239 patients was 36.7 months. Forty (16.7%) had died of their disease, 23 (9.6%) are alive with systemic disease, and 165 (69.0%) are disease free at median follow-up of 33 months. Eleven patients have died of other causes and have been censored for the analysis. Twenty patients (8.4%) have had a local recurrence.

Figures 1a and 1b show the Kaplan-Meier estimates of the survivor functions of time to local recurrence stratified by margin and status of the local tumor site with log-rank test statistics and *P*-values. This univariate analysis suggests that time to local recurrence is: (1) decreased with margin positive surgery ($\chi^2 = 18.30$, $P < 0.00001$; and (2) decreased following unplanned resection with microscopic disease found in the reresection specimen ($\chi^2 = 8.83$, $P = 0.01$). From Figure 1a it can be seen that the local recurrences occur in the early period following margin positive surgery, with the largest effect appearing to occur in the first 2 years. Figure 1b demonstrates that the group presenting with a mass in situ or reexcised with no tumor found in the resection specimen have a better outcome than those reexcised and found to have tumor in their reresection specimen. Again, the risk period for this variable was greatest in the early period following surgery.

**TABLE I. Unplanned Resection for Soft Tissue Sarcoma of the Extremity: Characteristics of the Study Sample (n = 239)**

| |
|---|
| Age: mean = 56.2, S.D. = 18.9, range is 15 to 94 |
| Gender: males = 123 (51.5%), females = 116 (48.5%) |
| Site of tumor: shoulder girdle/shoulder = 39 (16.3%) |
| elbow = 23 (9.6%) |
| distal forearm/wrist/hand = 12 (5.0%) |
| pelvis/hip = 69 (28.9%) |
| knee = 79 (33.1%) |
| distal leg/ankle/foot = 17 (7.1%) |
| Presenting status: primary = 202 (84.5%), local recurrence = 37 (15.5%) |
| Subtype: malignant fibrous histiocytoma = 93 (38.9%) |
| liposarcoma = 64 (26.7%) |
| fibrosarcoma = 9 (3.8%) |
| synovial sarcoma = 15 (6.3%) |
| neurosarcoma = 9 (3.8%) |
| clear cell = 2 (0.8%) |
| epitheliod = 5 (2.1%) |
| dermatofibrosarcoma protuberans = 11 (4.6%) |
| aveolar soft part = 3 (1.3%) |
| angiosarcoma = 1 (0.4%) |
| leiomysarcoma = 14 (5.9%) |
| malignant haemangiopericytoma = 4 (1.7%) |
| extraskeletal chondrosarcoma = 3 (1.3%) |
| not otherwise specified = 7 (2.9%) |
| Grade: low = 47 (19.7%), high = 192 (80.3%) |
| Radiation: none = 53 (22.1%) |
| preoperative only = 95 (39.8%) |
| postoperative only = 55 (23.0%) |
| preoperative and postoperative boost = 36 (15.1%) |
| Prior surgery: no, mass in situ = 135 (56.5%) |
| yes, tumor found in reexcision specimen = 42 (17.6%) |
| yes, no tumor found in reexcision specimen = 62 (25.9%) |
| Size: by maximum diameter: mean = 7.5 cm, median = 6, S.D. = 5.8, range is 0.5 to 35 |
| per American Joint Committee on Cancer: ⩽5 cm = 133 (55.6%), >5 cm = 106 (44.4%) |
| Depth: superficial = 52 (21.8%), deep = 187 (78.2%) |
| Margin: negative = 194 (81.2%), microscopic positive = 45 (18.8%) |
| Local recurrence: no = 219 (91.6%), yes = 20 (8.4%) |
| Systemic relapse: no = 175 (73.2%), yes = 64 (26.8%) |
| Status at last follow-up: Alive with no evidence of disease = 165 (69.0%) |
| Alive with evidence of disease = 23 (9.6%) |
| Dead of disease = 40 (16.7%) |
| Deceased of other causes = 11 (4.6%) |
| Follow-up time: mean = 36.8 months, median = 31 months, S.D. = 23.9, [a]range = 2 to 112 |

[a]Some cases are less than 2 years follow-up as they died of metastases. These cases would have the effect of relatively decreasing the risk ratio for local recurrence.

Exploration of nonproportional hazards using the likelihood ratio test indicated that there was violation of the proportional hazard assumption for both margin and prior surgery ($\chi^2 = 60.63$, $P < 0.00001$, and $\chi^2 = 26.53$, $P < 0.00001$, respectively). Consequently, the time-dependent covariate for both margin and prior surgery was included in the multivariate analysis. Table II presents the results for the Cox model. The largest effect was for positive margin resection, although this effect decayed over the follow-up time. There was also a large effect for reexcision surgery when tumor was found in the specimen after controlling for margin, and this effect also decayed over time.

In an exploratory analysis, we evaluated tumor grade (low vs. high grade), size, and depth. Grade ($\chi^2 = 0.55$, $P = 0.46$), size ($\chi^2 = 0.33$, $P = 0.57$), and depth ($\chi^2 = 0.76$, $P = 0.38$) were not significant in univariate analysis using the log-rank test and were not tested in the multivariate model.

## DISCUSSION

The finding in this study that positive margins of resection contribute to the risk of local relapse despite the use of adjuvant radiotherapy confirms an earlier retrospective analysis done by our group [2] as well as by other investigators [3,4,7–9]. We concur with Sadoski et al. [8] that margins are best characterized by the simple question: "Is tumor evident anywhere at the margin of resection?" The presence of tumor at the margin is the most important risk factor for local recurrence and is generally recognized as important [3,4,7–9]. However, despite the efforts of several investigators to determine risk factors for local relapse in soft tissue sarcoma [1,3, 4,7–9,15], the effect of unplanned resection on the risk of local relapse has not, to our knowledge, been previously evaluated using multivariate analysis, and this finding requires further discussion.

The categorization of the status of the local tumor site at definitive surgery into three levels: tumor in situ; prior unplanned resection with microscopic disease identified in the reexcision specimen; and prior unplanned resection with no microscopic disease in the reexcision was based a priori on empirical clinical judgment. The first consideration was whether the patient had undergone unplanned resection prior to referral to our center. The second consideration was whether tumor was identified in the scar tissue from the previous surgery in those patients who had prior unplanned resection. If a patient is referred with the tumor in situ (either without prior surgery or following incisional biopsy) the surgeon can assess the extent of tumor spread into the surrounding tissue using imaging studies, and perhaps even more importantly, by palpation of the tissue at the time of resection. However, if the gross tumor mass has been completely excised, the surgeon has neither imaging nor tactile evidence of tumor extent. In addition, the surgeon cannot determine exactly the extent of tissue dissection undertaken by the referring surgeon and, therefore, has little concept of the distance from the wound that may be contaminated by cancer cells. Based on these features we determined that there was validity to the concept of categorizing patients

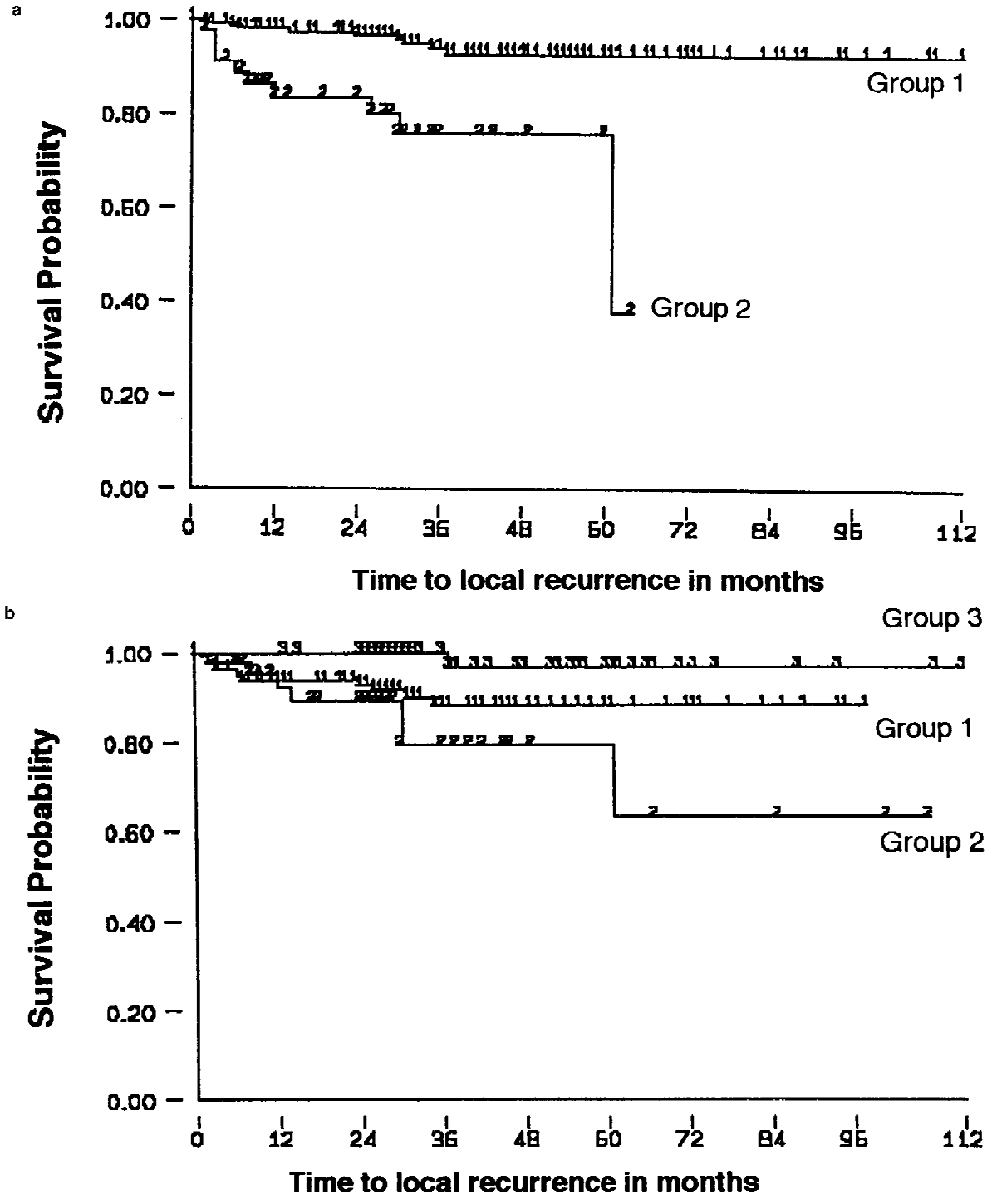


Fig. 1. Kaplan-Meier estimates of local control. **(a)** Surgical margins. Group 1, negative margins; Group 2, positive margins. **(b)** Prior surgical groups. Group 1, no prior surgery; Group 2, prior surgery, tumor found; Group 3, prior surgery, no tumor found.

as to whether unplanned resection had been performed prior to definitive surgery.

The rationale for categorizing the reexcision cases is further supported by pathology studies of specimens obtained following reresection in patients treated with unplanned resections prior to referral [4–6,11,12]. They have generally tended to find a higher incidence of residual disease than our group has identified; we have identified microscopic disease in 35 to 40% of cases. Goodman et al. [11], Giuiliano and Eilber [10], and Peabody et al. [6] found evidence of residual disease in about one-half of patients treated with prior unplanned resec-

**TABLE II. Results of Multiple Regression Modelling of Extremity Soft Tissue Sarcoma Patients Treated by Limb-Sparing Surgery (n = 239) Using the Cox Model**

| Variable | Coefficient | Standard error | *P*-value | Hazard ratio |
|---|---|---|---|---|
| Margin: | | | | |
| positive margin | 4.96 | 1.31 | 0.000 | dependent on time |
| margin*log (time) | −1.55 | 0.44 | 0.001 | |
| Prior unplanned resection, microscopic disease found | 1.91 | 1.08 | 0.05 | dependent on time |
| Prior unplanned resection, no microscopic disease found | 2.36 | 3.00 | 0.43 | |
| Prior surgery *log (time) | −0.52 | 0.40 | 0.20 | |

tion, and Karakousis et al. [4] found residual sarcoma in 91% of patients reexcised without prior irradiation.

This difference in the frequency of residual disease may relate to several factors. We have not characterized patients as having unplanned resections if there was residual mass disease evident on physical examination or on imaging [16]. Some of these cases may have been included in calculations related to residual disease by other investigators. Some of our patients treated following prior unplanned resections were treated with preoperative radiation, and this can complicate the pathological assessment of the resection specimen for the presence of residual disease [17]. We are encouraged by the identification of residual disease provided by our pathologists, as there has been only one case of local relapse in the 62 extremity patients found to have no residual disease following unplanned resection. Twenty-eight of these 62 patients received no treatment other than reexcision of the previously excised tumor bed (i.e., they received no radiotherapy).

The data from the current investigation shows that a finding of tumor in the reexcision sample following an unplanned resection is a very important risk factor for local relapse. When no tumor was found in the specimen removed for reexcision following unplanned resection (62 patients), only one patient has suffered a local relapse. On the other hand, when sarcoma was found on pathological review of the reresection sample, 7 of 42 patients suffered a recurrence. The results of the study of Gustafson et al. [12] would also support our findings that there is an increased risk of local recurrence in patients referred for reexcision of soft tissue sarcoma.

The difference in the risk of local relapse between reexcision patients with residual microscopic disease in their specimen vs. those found to harbor no microscopic disease may be related to the extent of the initial unplanned resection or may be due to the inherent characteristics of the sarcoma. Prior to advising reexcision of the tumor bed following an unplanned resection, we first determined that the initial resection margins were positive for the presence of microscopic disease. However, we recognized that there would be variability in the extent of microscopic disease left following unplanned resection. In some cases, more complete resection would leave minimal microscopic residual disease that could not be identified microscopically, and this disease burden might be so small that it was unlikely to result in local recurrence. Alternately, the identification of tumor in the reresection specimen might be the result of a more aggressive phenotype of the tumor that was more likely to proliferate and spread through the scar and be identified on pathological analysis. Either of these explanations would account for the increased risk of recurrence in the group with identifiable tumor after unplanned excision.

It is possible to make two suggestions regarding the management of soft tissue sarcoma from analysis of this data. The first suggestion is that soft tissue sarcoma should be excised with negative margins, and the second message is that unplanned excisions complicate management and should be avoided. Resection of soft tissue sarcoma with negative margins may be technically difficult and should generally be undertaken by surgeons trained in this subspecialized field. In some cases, positive microscopic resection margins are inevitable in limb-sparing surgery (18% of cases in this study had positive definitive resection margins). We have shown in a prior study that the risk of positive margins is increased in patients treated after an initial unplanned resection [13].

The goal of avoidance of unplanned resections should be achievable. This is an issue of importance for clinical education and requires a higher level of clinical suspicion in physicians treating soft tissue masses arising in the extremity. Surgeons treating patients with soft tissue extremity lesions should recognize that the initial management of these cases can determine the eventual risk of local recurrence. The unplanned excision can be avoided by recognizing that all subfascial masses and large subcutaneous masses should undergo imaging and incisional or needle biopsy prior to removal. Deep or large subcutaneous lesions have a high risk of malignancy and imaging, and biopsy of these lesions should be undertaken prior to resection.

## CONCLUSIONS

Two variables were identified that contributed to the risk of local relapse in soft tissue sarcoma of the extremity: (1) resection with microscopic evidence of tumor at

the resection margin; and (2) a history of unplanned resection prior to referral with residual sarcoma found in the resection of the tumor bed.

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